C–H Borylation

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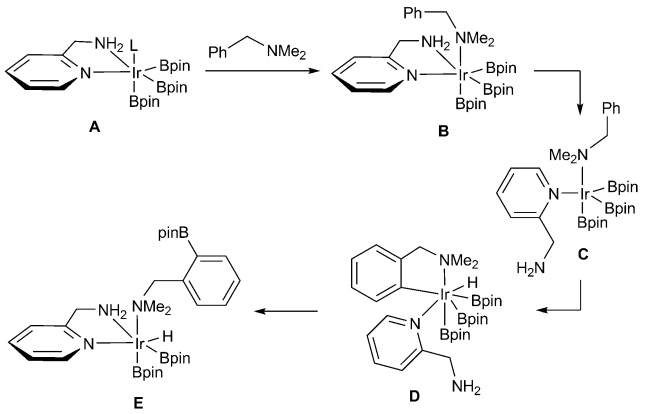
# Phosphine-Directed C–H Borylation Reactions: Facile and Selective Access to Ambiphilic Phosphine Boronate Esters**

*Kristina M. Crawford, Timothy R. Ramseyer, Christopher J. A. Daley, and Timothy B. Clark**

***Abstract:*** *Ambiphilic ligands have received considerable attention over the last two decades due to their unique reactivity as organocatalysts and ligands. The iridium-catalyzed C–H borylation of phosphines is described in which the phosphine is used as a directing group to provide selective formation of arylboronate esters with unique scaffolds of ambiphilic compounds. A variety of aryl and benzylic phosphines were subjected to the reaction conditions, selectively providing stable, isolable boronate esters upon protection of the phosphine as the borane complex. After purification, the phosphine-substituted boronate esters could be deprotected and isolated in pure form.*

Tertiary phosphines have played a prominent role in the field of organometallic chemistry based on their ability to serve as ancillary ligands in a plethora of homogeneous catalysis reactions.[1–5] The wide variety of steric and electronic properties that are available with commercially and readily accessible phosphines has facilitated their practical use.[1,6–8] New applications of trivalent phosphines continue to be explored in metal-catalyzed reactions and frustrated Lewis pair (FLP) chemistry.[9,10] Recent interest in ambiphilic organocatalysts and ligands[11] has led to a number of intriguing catalytic systems for small-molecule activation and reaction. Phosphine-substituted boranes and boronate esters are particularly noteworthy for their application as organocatalysts or ligands in metal-catalyzed transformations.[12] In spite of the promising reactivity of these compounds, a limited variety of scaffolds have been explored due to the inability to readily access such molecular structures under the current methods.

Based on the preliminary work by our group and others in the area of substrate-directed arene C–H borylation,[13–21] we became interested in expanding this methodology to phosphines,[22] simplifying access to valuable phosphine building blocks and organocatalysts. Current methods to achieve substrate-directed C–H borylation reactions utilize silanes,[14,17] esters,[15,16] amides,[15] ethers,[15] halides,[15] and nitrogen-containing functional groups[13,18–21] as directing groups. There have been several different approaches to achieving these directing effects ranging from hydrogen bonding interactions between the substrate and the boronate ester oxygen[21] to Lewis-base-directed activation using hemilabile diamine ligands.[19,20] We have used this latter approach, as have Fernández and Lassaletta, to achieve complimentary selectivity to the typical rigid ligands of 4,4′-di-*tert*-butylbipyridine and substituted phenanthrolines, which are largely controlled by steric congestion at the arene C–H bond.[23–25] Flexible diamine ligands have been proposed to undergo facile dissociation of one arm of the bidentate ligand to allow for the required C–H activation step on the otherwise coordinatively saturated iridium complex (Scheme 1, **B** to **C**).[19,20] A critical step in this type of catalysis relies on the ability of the diamine ligand to displace the borylated substrate to allow catalyst turnover. We reasoned that appropriately chosen bidentate ligands could effectively displace a phosphine-bound substrate and allow catalyst turnover under otherwise similar reaction conditions. We herein report the directed C–H borylation of tertiary phosphines to provide phosphine-substituted arylboronate esters in high yield and selectivity.




***Scheme 1.*** Proposed mechanism of amine-directed C–H borylation with hemi-labile ligands.

Initial reaction conditions were probed with benzyldiphenylphosphine as the substrate and an array of diamine and aminophosphine ligands [Eq. (1), Table 1]. Several diamine ligands provided an appreciable amount of desired C–H borylation product **1a** (entries 1–3), but the low conversions were not significantly improved by standard ligand modifications. Aminophosphine ligands also provided modest conversion (entries 4, 5). Upon examination of the reaction

[*] K. M. Crawford, T. R. Ramseyer, C. J. A. Daley, T. B. Clark
University of San Diego
San Diego, CA (USA)
E-mail: clarkt@sandiego.edu

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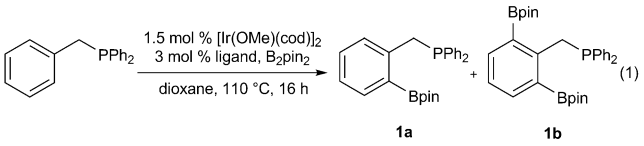
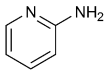
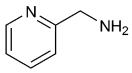
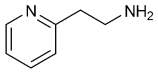
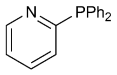
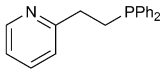


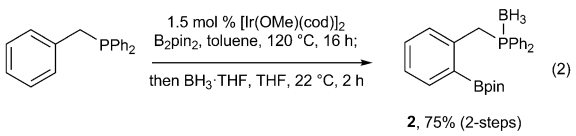

***Table 1:*** Ligand screen of phosphine-directed borylation.

| Entry | Ligand | Conversion [%][a] | **1a**:**1b**[b] |
|---|---|---|---|
| 1 |  | 39 | 96:4 |
| 2 |  | 37 | 92:8 |
| 3 |  | 39 | 93:7 |
| 4 |  | 33 | 80:20 |
| 5 |  | 43 | 98:2 |
| 6 | none | 96 | 71:29 |
| 7[c] | none | 87 | 96:4 |

[a] The conversion was determined by $^1$H NMR spectroscopy using a 5 s relaxation delay to insure integral integrity. All conversions are based on the arene substrate. [b] Ratio of **1a**/**1b** was determined by $^1$H NMR spectroscopy. [c] Conditions: toluene, 110 °C, 16 h.

without added ligand, a significant boost in conversion was observed, leading to nearly full conversion to **1a**/**1b**, albeit with poor selectivity of **1a**/**1b** (71:29). After a brief solvent screen, toluene was found to provide an 87% conversion to the borylated products with a 96:4 selectivity of **1a**/**1b** (entry 7);[26] *meta* and *para* isomers were undetectable by $^1$H NMR spectroscopy under all of the reaction conditions examined. The ability to use toluene as a solvent also demonstrates the significant reactivity increase imparted by the phosphine directing group which leads to selective C–H functionalization over that of toluene, which is present in a much higher concentration.[20]

To facilitate isolation and purification of the resulting air-sensitive boronate ester, the phosphine was protected as the borane complex **2**,[27] providing an air-stable crystalline product [Eq. (2)]. Purification of **2** by flash column chromatography provided analytically pure product in 75% yield and the identity of the major borylation product was confirmed by X-ray crystallography (Figure 1).




The effect of the phosphine substituents on substrate reactivity and selectivity (for mono-*ortho* borylation) was investigated with dicyclohexyl- and diadamantyl-substituted

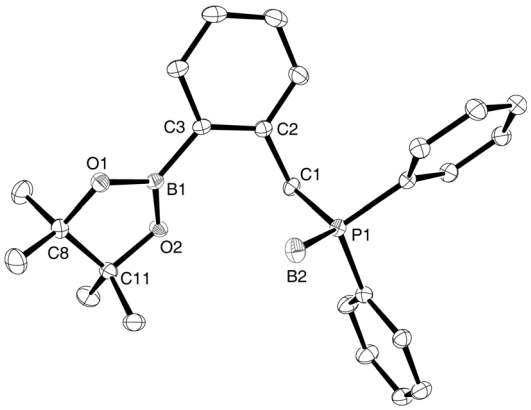
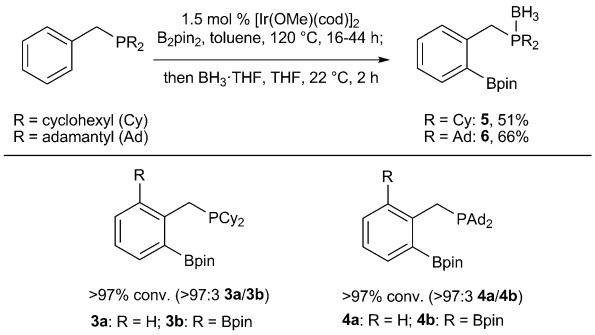



***Figure 1.*** X-ray crystallographic structure of **2**. Ellipsoids are shown at 50% probability. Hydrogen atoms are omitted for clarity.




***Scheme 2.*** Effect of phosphine substituent on borylation reactivity and selectivity.

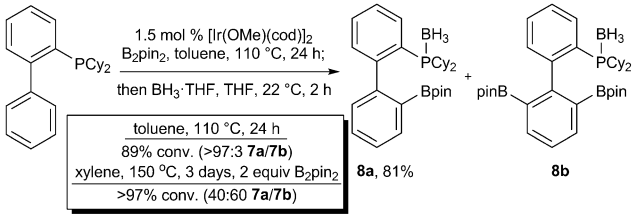
benzylphosphines (Scheme 2). Benzyldicyclohexylphosphine required increased reaction times (44 h) compared to the diphenyl analogue but resulted in >97% conversion to borylated product **3a**; improved selectivity for the monosubstituted product (>97:3 **3a**/**3b**) was also observed. Benzyldiadamantylphosphine also demonstrated improvement in selectivity (>97:3 **4a**/**4b**) and conversion (>97% conv.) with a 16 h reaction time. The increased reaction rate for the more sterically hindered diadamantyl substrate likely results from an increased rate of dissociation of the sterically hindered phosphine of **4** from the iridium catalyst upon borylation. Both **3a** and **4a** were isolated in moderate to good yields as the corresponding borane complexes **5** and **6**. In spite of high conversions in the C–H borylation reaction and clean formation of the borane complex, a moderate yield is obtained in some cases due to challenges in the isolation of the resulting protected boronate esters.

To expand the scope of substrates that could be used under these reaction conditions, several arylphosphines were explored. Triphenylphosphine was unreactive under the conditions, likely due to the inability to form the requisite 4-membered metallocycle upon directed C–H activation (or the related σ-bond metathesis transition state).[28–30] In contrast, 2-(dicyclohexylphosphino)biphenyl provided the desired borylation product (**7a**, precursor to **8a** prior to borane protection) in good conversion and selectivity

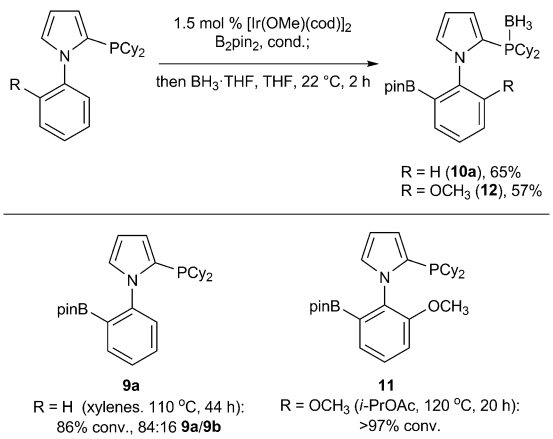
  

(Scheme 3, >97:3 **7a**/**7b**). Borane complex **8a** was obtained in an 81% yield of the isolated product.

During the screening of reaction solvents and temperatures with 2-(dicyclohexylphosphino)biphenyl the level of




***Scheme 3.*** Directed C–H borylation of 2-(dicyclohexylphosphino)biphenyl.



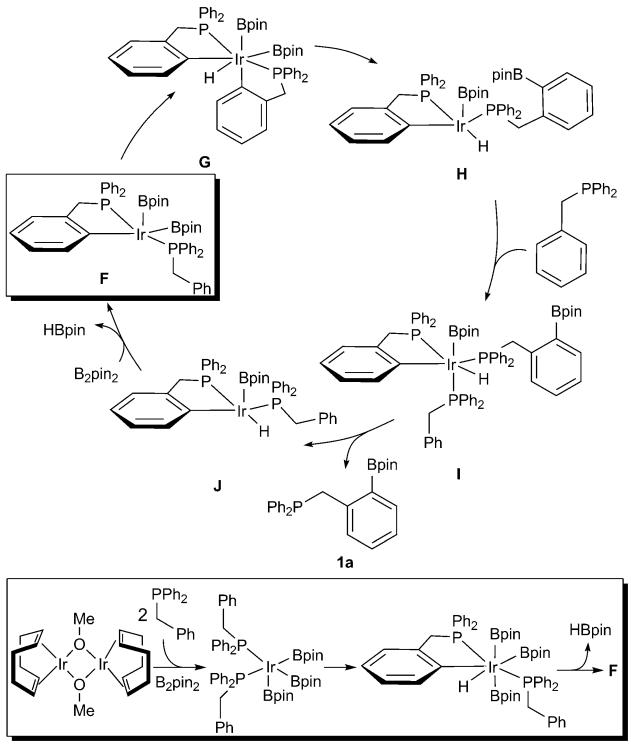

***Scheme 4.*** C–H borylation of pyrrole-containing phosphines.

selectivity for **7a** over **7b** varied significantly. With an interest in accessing the bisborylated product, two equivalents of bis(pinacolato)diboron were added to the phosphine in xylenes and heated to 150 °C for 3 days, resulting in >97% conversion and a 40:60 ratio of **7a**/**7b**. The borane complex of **7b** was obtained in modest yield (25%) after flash column chromatography and recrystallization to provide **8b** in pure form (Scheme 3). Although the yield of **8b** was low, this bisborylated product has intriguing potential for ligand synthesis and will be the subject of further study.

Unlike the consistent reactivity observed with sterically encumbered benzylphosphines (see above), biphenyl-derived phosphines were much more sensitive to sterically encumbered phosphine substituents. 2-(Di-*tert*-butylphosphino)biphenyl, for example, was found to be unreactive using several reaction solvents and increased reaction temperatures (<5% borylation product formed). The increased steric congestion, in this case, is believed to block formation of the active catalyst (see below).

Directed C–H borylation of *N*-arylpyrrole phosphines from the cataCXium class of ligands was pursued next to provide intriguing analogues of these valuable ligands.[31] Iridium-catalyzed C–H borylation of *N*-phenyl-2-(dicyclohexylphosphino)pyrrole [cataCXium PCy] in *m*-xylenes as solvent (at 110 °C for 44 h) provided the best combination of conversion (86%) and selectivity of monoborylation product **9a** (84:16 **9a**/**9b**, Scheme 4). Borane complex **10** was obtained in a 65% yield of isolated product as a mixture of mono- and bis-borylated products. C–H borylation of 2-(dicyclohexylphosphino)-1-(2-methoxyphenyl)-1*H*-pyrrole [cataCXium POMeCy] was found to give optimal conversion (>97%) to **11** in isopropylacetate at 120 °C for 20 h, providing **12** as the borane complex in 57% isolated yield.

Building from the generally accepted mechanism[28–30] for arene C–H borylation a plausible catalytic cycle is outlined in Scheme 5. Formation of the active catalyst is the most distinct aspect of this mechanism (Scheme 5, bottom), requiring C–H activation of the substrate, which subsequently serves as a ligand, and is anchored to the iridium complex. Notably, there are numerous examples of phosphine-directed C–H activation of analogous substrates by iridium complexes in the literature to support the feasibility of these intermediates.[32–35] The proposed catalytically active complex is a bisboryl iridium(III) complex (**F**), rather than the generally accepted trisboryl complex due to the bidentate ligand serving as an LX-type ligand.[36] Since one of the boryl substituents is replaced by a carbon-based X ligand, the coordination of a second phosphine does not lead to a coordinatively saturated iridium complex. 16-electron complex **F**, therefore, does not require partial dissociation of one arm of the bidentate ligand, which is the proposed key step of nitrogen-directed C–H borylation with hemi-labile ligands.



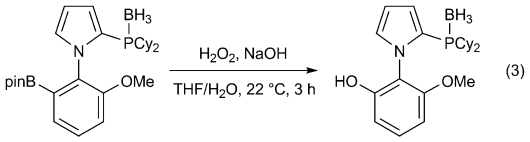

***Scheme 5.*** Proposed catalytic cycle of C–H borylation.

The major difference between this mechanism and one requiring hemi-labile ligands[19,20] is the role of the phosphine as both substrate and ligand. Since the mechanism requires

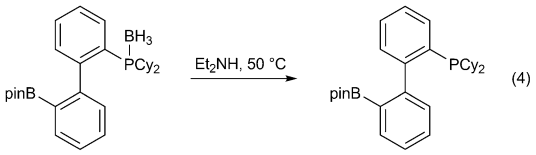
facile C–H activation of the substrate/ligand in order to enter into the catalytic cycle, the nature of the substrate is going to play a key role in whether a catalytically active species will form. In the case of 2-(di-*tert*-butylphosphino)biphenyl, the added steric congestion of the *tert*-butyl substituents causes a significant increase in the transition state energy of the initial C–H activation step to form the catalytically active species. Since the active catalyst is inaccessible, the starting material is left unreacted rather than showing slow formation of product. A full study of the reaction mechanism will be initiated to understand the details of the reaction and ultimately expand the substrate scope.

Numerous potential transformations are envisioned with the borylated phosphines described above utilizing the carbon–boron bond.[37] To demonstrate an example of the utility of these synthetic intermediates, the oxidation of **12** was achieved [Eq. (3)], providing alcohol **13** in 69% isolated yield.[38,39] Additional transformations involving the versatile C–B bond that tolerate the protected phosphine to access complex phosphines are currently underway.




**12** **13**, 69%

The recent attention given to ambiphilic ligands/catalysts, and in particular those utilizing boron as a remote Lewis acid, is another area of interest for these borylated phosphines.[11,12] To this end, deprotection of the phosphine in the presence of the boronate ester was investigated [Eq. (4)]. Phosphine-borane complex **8a** was treated with diethylamine at 50 °C to provide deprotected phosphine **7a** in high yield and purity.[40]




**8a** **7a**, 85%

In summary, substrate-directed C–H borylation of benzylic and aryl phosphines using a commercially available iridium catalyst has been described. The borylation is selective for an adjacent C–H bond and generally provides high selectivity for monoborylation over bisborylation. The resulting boronate esters were protected as the phosphine-borane complex to allow purification. The protecting group is readily removed, providing a potential new route to a variety of ligand scaffolds. The mechanism of the reaction is proposed to involve the initial formation of a P,C-bound bidentate ligand by C–H activation of the substrate, followed by Lewis base-directed C–H activation and borylation of the remaining substrate.

## Experimental Section

General procedure for C–H borylation/borane protection: To a 50 mL PTFE-valved reaction tube, equipped with a stir bar and charged with $[Ir(\mu\text{-OMe})(cod)]_2$ (0.004 g, 0.015 mmol), was added $B_2pin_2$ (0.102 g, 0.400 mmol), the phosphine (0.400 mmol), and toluene (1.0 mL). After heating (110–150 °C), the reaction mixture was transferred to a scintillation vial in an inert atmosphere glovebox and the volatiles were removed in vacuo. The crude reaction mixture was removed from the glovebox and subjected to positive nitrogen pressure. Degassed THF (2 mL) was added and the reaction vessel was placed in a 0 °C bath. A solution of $BH_3$·THF (0.8 mL, 1.0 M solution in THF, 0.800 mmol) was added dropwise. The reaction vessel was removed from the bath and warmed to ambient temperature. After 2 h the volatiles were removed in vacuo. Purification by silica gel flash column chromatography provided the corresponding phosphine-substituted arylboronate ester.

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[1] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.
[2] C. J. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407.
[3] K. N. Gavrilov, A. I. Polosukhin, *Russ. Chem. Rev.* **2000**, *69*, 661–682.
[4] D. H. Valentine, Jr., J. H. Hillhouse, *Synthesis* **2003**, 2437–2460.
[5] *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis* (Eds.: P. C. J. Kamer, P. W. N. M. van Leeuwen), Wiley, Chichester, **2012**.
[6] C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2956–2965.
[7] D. White, B. C. Tavener, P. G. L. Leach, N. J. Coville, *J. Organomet. Chem.* **1994**, *478*, 205–211.
[8] Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2003**, 1890–1901.
[9] D. W. Stephan, *Org. Biomol. Chem.* **2008**, *6*, 1535–1539.
[10] D. W. Stephan, G. Erker, *Angew. Chem.* **2010**, *122*, 50–81; *Angew. Chem. Int. Ed.* **2010**, *49*, 46–76.
[11] a) M. Kanai, N. Kato, E. Ichikawa, S. Masakatsu, *Synlett* **2005**, 1491; b) D. B. Grotjahn, *Dalton Trans.* **2008**, 6497; c) M. Emmert, G. Kehr, R. Fröhlich, G. Erker, *Chem. Eur. J.* **2009**, *15*, 8124; d) B. E. Cowie, D. J. H. Emslie, H. A. Jenkins, J. F. Britten, *Inorg. Chem.* **2010**, *49*, 4060; e) R. H. Crabtree, *New J. Chem.* **2011**, *35*, 18; f) O. Tutusaus, C. Ni, N. K. Szymczak, *J. Am. Chem. Soc.* **2013**, *135*, 3403.
[12] a) H. Braunschweig, R. Dirk, B. Ganter, *J. Organomet. Chem.* **1997**, *545–546*, 257; b) L. Turculet, J. D. Feldman, T. D. Tilley, *Organometallics* **2004**, *23*, 2488; c) S. Bontemps, G. Bouhadir, K. Miqueu, D. Bourissou, *J. Am. Chem. Soc.* **2006**, *128*, 12056; d) A. J. M. Miller, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **2008**, *130*, 11874; e) A. Fischbach, P. R. Bazinet, R. Waterman, T. D. Tilley, *Organometallics* **2008**, *27*, 1135; f) J. Vergnaud, M. Grellier, G. Bouhadir, L. Vendier, S. Sabo-Etienne, D. Bourissou, *Organometallics* **2008**, *27*, 1140; g) S. Bontemps, G. Bouhadir, D. C. Apperley, P. W. Dyer, K. Miqueu, D. Bourissou, *Chem. Asian J.* **2009**, *4*, 428; h) O. Baslé, S. Porcel, S. Ladeira, G. Bouhadir, D. Bourissou, *Chem. Commun.* **2012**, *48*, 4495; i) M.-A. Courtemanche, M.-A. Légaré, L. Maron, F.-G. Fontaine, *J. Am. Chem. Soc.* **2013**, *135*, 9326.

  

[13] S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2006**, *128*, 15552 – 15553.
[14] T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 7534 – 7535.
[15] S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura, *J. Am. Chem. Soc.* **2009**, *131*, 5058 – 5059.
[16] T. Ishiyama, H. Isou, T. Kikuchi, N. Miyaura, *Chem. Commun.* **2010**, *46*, 159 – 161.
[17] D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068 – 4069.
[18] S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* **2011**, *133*, 19310 – 19313.
[19] A. Ros, B. Estepa, R. López-Rodríguez, E. Álvarez, R. Fernández, J. M. Lassaletta, *Angew. Chem.* **2011**, *123*, 11928 – 11932; *Angew. Chem. Int. Ed.* **2011**, *50*, 11724 – 11728.
[20] A. J. Roering, L. V. A. Hale, P. A. Squier, M. A. Ringgold, E. R. Wiederspan, T. B. Clark, *Org. Lett.* **2012**, *14*, 3558 – 3561.
[21] P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2012**, *134*, 11350 – 11353.
[22] For an example of phosphorus-directed C–H borylation using borenium cations, see: C. Cazorla, T. S. De Vries, E. Vedejs, *Org. Lett.* **2013**, *15*, 984 – 987.
[23] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890 – 931.
[24] J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992 – 2002.
[25] S. M. Preshlock, B. Ghaffari, P. E. Maligres, S. W. Krska, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2013**, *135*, 7572 – 7582.
[26] Treatment of benzyldiphenylphosphine with 1 equivalent of HBpin in place of $B_2pin_2$ resulted in a 90% conversion with an 90:10 selectivity of **1a**/**1b**. The decreased selectivity led us to focus on the use of $B_2pin_2$ for these reactions.
[27] J. M. Brunel, B. Faure, M. Maffei, *Coord. Chem. Rev.* **1998**, *178 – 180*, 665 – 698.
[28] H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, *125*, 16114 – 16126.
[29] T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263 – 14278.
[30] B. A. Vanchura II, S. M. Preshlock, P. C. Roosen, V. A. Kallepalli, R. J. Staples, R. E. Maleczka, Jr., D. A. Singleton, M. R. Smith III, *Chem. Commun.* **2010**, *46*, 7724 – 7726.
[31] A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen, M. Beller, *Chem. Commun.* **2004**, 38 – 39.
[32] J.-Y. Hung, C.-H. Lin, Y. Chi, M.-W. Chung, Y.-J. Chen, G.-H. Lee, P.-T. Chou, C.-C. Chen, C.-C. Wu, *J. Mater. Chem.* **2010**, *20*, 7682 – 7693.
[33] C.-H. Lin, Y.-C. Chiu, Y. Chi, Y.-T. Tao, L.-S. Liao, M.-R. Tseng, G.-H. Lee, *Organometallics* **2012**, *31*, 4349 – 4355.
[34] For a review on cyclometalation reactions, see: M. Albrecht, *Chem. Rev.* **2010**, *110*, 576.
[35] S. Hietkamp, D. J. Stufkens, K. Vrieze, *J. Organomet. Chem.* **1979**, *168*, 351 – 361.
[36] J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Mill Valley, **2010**.
[37] *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*, *Vol. 1* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2011**.
[38] For an example of a synthetic protocol to access hydroxybiphenyl-based phosphine ligands, see: G. Keglevich, A. Kerényi, H. Szelke, K. Ludányi, T. Körtvélyesi, *J. Organomet. Chem.* **2006**, *691*, 5038.
[39] For an example of a hydroxybiphenyl-based phosphine serving as an organocatalyst in a domino reaction, see: X. Meng, Y. Huang, R. Chen, *Org. Lett.* **2009**, *11*, 137.
[40] T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244 – 5252.

  